Fact Sheet for Health Care Providers: Interpreting Results from the Aptima® Zika Virus assay

September 7, 2016

Dear Health Care Provider:

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to authorize the use of the Aptima® Zika Virus assay on the Panther System instrument for the *in vitro* qualitative detection of RNA from Zika virus in human serum, plasma and urine (collected alongside a patient-matched serum or plasma specimen). Testing should be conducted only on specimens from individuals meeting Centers for Disease Control and Prevention (CDC) Zika clinical and/or epidemiological criteria for testing (http://www.cdc.gov/zika/hc-providers/index.html) by laboratories in the United States that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, to perform high complexity tests, or by similarly qualified non-U.S. laboratories.

FDA issued this EUA based on data submitted to FDA, and on the U.S. Secretary of Health and Human Services' (HHS) declaration that circumstances exist to justify the emergency use of *in vitro* diagnostic tests for the detection of Zika virus and/or diagnosis of Zika virus infection. This EUA will terminate when the HHS Secretary's declaration terminates, unless FDA revokes it sooner.

The information in this Fact Sheet is to inform you of the significant known and potential risks and benefits of the emergency use of the Aptima® Zika Virus assay. For more information on this EUA, please see FDA's website at: http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm.

Why is this test needed at this time?

Public health officials have determined that Zika virus poses a potential public health emergency. Zika virus transmission has occurred primarily through the bite of infected *Aedes* species mosquitoes. Zika virus can also be transmitted from mother to fetus during pregnancy, through blood transfusion, and through sexual transmission from infected individuals to their sexual partners.

At this time, there are no FDA approved/cleared tests available that can detect Zika virus in clinical specimens in the United States. Hologic, Inc. has developed the Aptima® Zika Virus assay to detect evidence of Zika virus infection. Current information on Zika virus infection for health care providers, including case definitions, is available at: http://www.cdc.gov/zika/hc-providers/index.html. All information and guidelines, including those on Zika virus laboratory testing, may change as more data are gathered on this virus. Please check CDC's Zika virus website regularly for the most current information (http://www.cdc.gov/zika/index.html).

If Zika virus infection is suspected based on current clinical and/or epidemiological criteria recommended by public health authorities, the Aptima® Zika Virus assay may be ordered. As chikungunya virus infection and dengue virus infection can have early symptoms resembling those of Zika virus infection, and co-infection with these viruses is possible, in addition to testing for Zika virus, testing should be considered for chikungunya and dengue. Please contact your state or local health department to facilitate testing.

The results should be used in conjunction with clinical signs and symptoms, epidemiological information and travel history to diagnose Zika virus infection. This test is authorized for use with serum, plasma and urine (when submitted alongside a patient-matched serum or plasma sample). Health care providers are strongly encouraged to collect and submit serum specimens alongside other authorized specimen types to provide additional opportunities for diagnosing Zika virus infection.

Based on available data as of September 7, 2016, serum is the primary diagnostic specimen and should be the priority specimen for collection and testing. Specimens should be collected with appropriate infection control precautions and according to the manufacturer's instructions for the specimen collection device. Additional guidance for collection of body fluid specimens for Zika diagnostic testing may be found at: http://www.cdc.gov/zika/hc-providers/body-fluids-collection-submission.html.

What are the symptoms of Zika virus infection?

Many people with Zika virus infection are asymptomatic. Symptomatic patients typically experience a mild illness characterized by fever, joint pain, rash, or conjunctivitis. Clinical illness is usually self-limited and lasts a week or less. Clinical illness recognition can be complicated in that not all symptomatic patients report all of these symptoms, and Zika manifestations overlap significantly with those seen in other viral infections. Although the exact incubation period is yet to be determined, it is considered to be about 3 days to 2 weeks.

Based on a review of available evidence, CDC has concluded that Zika virus infection in pregnancy is a cause of microcephaly (a birth defect characterized by small head size and impaired cranial and neural development in fetuses and infants) and other serious abnormalities of the brain in fetuses and infants. In addition, it has been linked to central nervous system injury, placental insufficiency, fetal growth restriction, fetal loss, eye abnormalities, and hearing impairment.[1,2]

Limited information is available currently about the spectrum of defects caused by prenatal Zika virus infection, the relative and absolute risks of adverse outcomes among fetuses whose mothers were infected at different times during pregnancy, and factors that might affect a woman's risk of adverse pregnancy or birth outcomes.

There are also reports of Guillain-Barré syndrome associated with Zika virus infection.

When should the Aptima® Zika Virus assay test be performed?

Zika virus RNA may be detected in serum and/or urine for up to 14 days following onset of symptoms. Persistence of Zika virus RNA detectable in urine is not well characterized but may be longer than in serum. For patients who are 2-12 weeks post-symptom onset, serologic testing should be considered. Test results should be used in conjunction with clinical signs and symptoms, epidemiological information and relevant travel history to diagnose Zika virus infection.

Specimens should be collected with appropriate infection control precautions and according to the manufacturer's instructions for the specimen collection device. Sera, collected in serum separator tubes or conventional serum collection tubes, should be centrifuged and separated from the cells or gel after collection to reduce the likelihood of hemolysis.

What does it mean if the specimen tests positive for Zika virus RNA?

A positive test for Zika Virus RNA indicates that RNA from Zika virus was detected in the patient's sample and is indicative of Zika virus infection. Laboratory test results should always be considered in the context of clinical observations and epidemiological data in making a final diagnosis and patient management decisions. For guidelines on Zika virus, please refer to http://www.cdc.gov/zika/hc-providers/index.html.

The Aptima® Zika Virus assay has been designed to minimize the likelihood of false positive test results. Cross-reactivity with other viruses, including chikungunya and other flaviviruses such as dengue and West Nile, is not expected. However, in the event of a false positive result, risks to patients could include any or all of the following: the impaired ability to detect and receive appropriate medical care for the true infection causing the symptoms, an unnecessary increase in the monitoring of a woman's pregnancy, or other unintended adverse effects.

All positive Zika virus test results should be reported to your local or state public health authorities. In the United States and its territories, Zika virus disease and congenital Zika virus infection are nationally notifiable diseases. For guidelines on Zika virus, please refer to http://www.cdc.gov/zika/hc-providers/index.html.

It should be emphasized that the identification of Zika virus infection in a pregnant woman does not provide any definitive information about the state of health of the fetus. Many questions remain about the impact of maternal Zika virus infection on the fetus, and the impact of factors such as timing, and the relevance of symptomatic versus asymptomatic infection. Detection of Zika virus RNA in specimens collected from the mother does not mean there is definite harm to the fetus.

What does it mean if the specimen tests negative for Zika virus RNA?

A negative test for Zika virus RNA in the specimen means that RNA from Zika virus is not present in the specimen above the test's limit of detection.

Given the reported transient, low-level viremia in many patients diagnosed with Zika virus infection, a negative result, especially if blood and/or urine testing is performed post 14 days of post symptom onset), does not exclude the possibility of Zika virus infection. Zika virus RNA negative results should not be used as the sole basis for treatment or other patient management decisions. The possibility of a false negative result should be considered if a patient's travel history and/or clinical illness raise suspicion of Zika infection. Such patients should be considered for serologic testing which is best performed 2-12 weeks after symptom onset.

For urine, it is especially important to note that this is not the primary diagnostic specimen type. Negative results in urine do not necessarily mean that an individual is not infected. When negative results are obtained for this specimen type, attention should be directed to the Aptima® Zika Virus assay result for the patient-matched serum or plasma specimen.

Further information on Zika virus infection for health care providers is available at http://www.cdc.gov/zika/hc-providers/index.html. Guidance for health care providers, including Health Care Providers Caring for Pregnant Women and Women of Reproductive Age with Possible Zika Virus Exposure is available on the CDC website: http://www.cdc.gov/zika/hc-providers/clinical-guidance.html.

Reporting Adverse Events

You should report adverse events, including problems with test performance or results, to MedWatch at http://www.fda.gov/medwatch, by submitting a MedWatch Form 3500 (available at https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home) or by calling 1-800-FDA-1088.

Pregnant patients should receive the *Fact Sheet for Pregnant Women: Understanding Results from the Aptima® Zika Virus assay.*

Give all other patients the *Fact Sheet for Patients: Understanding Results from the Aptima® Zika Virus assay*.

Contact Information for the Manufacturer:

Hologic, Inc.
10210 Genetic Center Drive
San Diego, CA 92121
Phone: +1-844-465-6442

E-mail: customersupport@hologic.com

Any significant new findings that negatively impact the performance of the test and that are observed during the course of the emergency use of the Aptima® Zika Virus assay will be made available at: http://www.hologic.com/.

References

1) Rasmussen, S.A., Jamieson, D.J., Honein, M.A., Petersen, L.R. Zika Virus and Birth Defects – Reviewing the Evidence for Causality. New England Journal of Medicine, April 12, 2016. DOI: 10.1056/NEJMsr1604338.
2) CDC Website - http://www.cdc.gov/zika/